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SOCS3
A novel therapeutic target for cardioprotection

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Abbreviations: AAV, adeno-associated virus; CIS, cytokine-inducible SH2 protein; CKO, cardiac-specific knockout; CT-1, cardiotrophin-1; CVB3, coxsackievirus B3; EPO, erythropoietin; G-CSF, granulocyte colony-stimulating factor; ERK1/2, extracellular-signal-regulated kinases 1 and 2; IFN, interferon; IL, interleukin; JAK, Janus kinase; KIR, kinase inhibitory region; KO, knockout; LIF, leukemia inhibitory factor; MI, myocardial infarction; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription

The suppressors of cytokine signaling (SOCS) family of proteins are cytokine-inducible inhibitors of Janus kinase (JAK)-signal transducer and activator of the transcription (STAT) signaling pathways. Among the family, SOCS1 and SOCS3 potently suppress cytokine actions by inhibiting JAK kinase activities. The generation of mice lacking individual SOCS genes has been instrumental in defining the role of individual SOCS proteins in specific cytokine pathways in vivo; SOCS1 is an essential negative regulator of interferon-γ (IFNγ) and SOCS3 is an essential negative regulator of leukemia inhibitory factor (LIF). JAK-STAT3 activating cytokines have exhibited cardioprotective roles in the heart. The cardiac-specific deletion of SOCS3 enhances the activation of cardioprotective signaling pathways, inhibits myocardial apoptosis and fibrosis and results in the inhibition of left ventricular remodeling after myocardial infarction (MI). We propose that myocardial SOCS3 is a key determinant of left ventricular remodeling after MI, and SOCS3 may serve as a novel therapeutic target to prevent left ventricular remodeling after MI. In this review, we discuss the signaling pathways mediated by JAK-STAT and SOCS proteins and their roles in the development of myocardial injury under stress (e.g., pressure overload, viral infection and ischemia).

Introduction

Cytokines play essential roles in the control of immunity, cell growth and differentiation and cell survival.[1,2] Some cytokines, including interleukins (ILs), interferons (IFNs) and hematopoietic growth factors, activate the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway.[3-5] The binding of a cytokine to its cell-surface receptor results in receptor dimerization and the subsequent activation of JAK tyrosine kinases. The activated JAKs phosphorylate the receptor cytoplasmic domains, creating docking sites for SH2-containing signaling proteins, including STATs. STATs are phosphorylated by JAKs, then dimerize and subsequently leave the receptor and translocate to the nucleus, where they activate gene transcription.[3-5] The JAK-STAT pathway can be negatively regulated at several steps through distinct mechanisms.[6-9] The suppressor of cytokine signaling (SOCS) family of proteins provide one of the major mechanisms for regulating cytokine signaling.[6-9] Negative-feedback regulation through SOCS proteins tightly regulates the duration and intensity of cytokine-induced JAK-STAT signaling (**Fig. 1**).[6-9]

SOCS1 was identified as a JAK-binding and STAT-inducible inhibitor of cytokine signaling pathways.[10-12] Among SOCS family proteins, SOCS1 and SOCS3 are structurally similar, and both of them strongly inhibit JAK kinase activity; however, their expression patterns and gene knockout (KO) phenotypes in mice are quite different. SOCS3 is induced by a variety of JAK-STAT-activating cytokines, including IL-6, granulocyte-colony stimulating factor (G-CSF), erythropoietin (EPO), cardiotrophin-1 (CT-1) and leukemia inhibitory factor (LIF).[13,14] In contrast, SOCS1 is strongly induced by IFNγ, especially in the lymphoid tissues.[15,16] SOCS3 knockout (SOCS3-KO) mice are embryonic lethal owing to a placental deficiency that can be rescued with a LIF receptor null background, suggesting that SOCS3 is an essential negative regulator of LIF-gp130 signaling.[13,14] SOCS1-KO mice exhibit stunted growth and die within 3 weeks after birth with systemic inflammation that can be abolished by an IFNγ null background, suggesting that SOCS1 is an essential negative regulator of IFNγ signaling during the neonatal phase.[15,16] Thus, SOCS1 and SOCS3 have essential roles in vivo roles regulating specific cytokine signaling pathways. To elucidate the tissue- or cell-specific roles of SOCS1 and SOCS3, we generated flox mice of SOCS1 and SOCS3.[17,18] Using these genetic mouse lines, we have revealed important roles for SOCS1 and SOCS3 in inflammation,[17,19,20] obesity,[21] atherosclerosis[22] and left ventricular remodeling after myocardial infarction (MI).[23] In this review, we will focus on the recent progress of SOCS1 and

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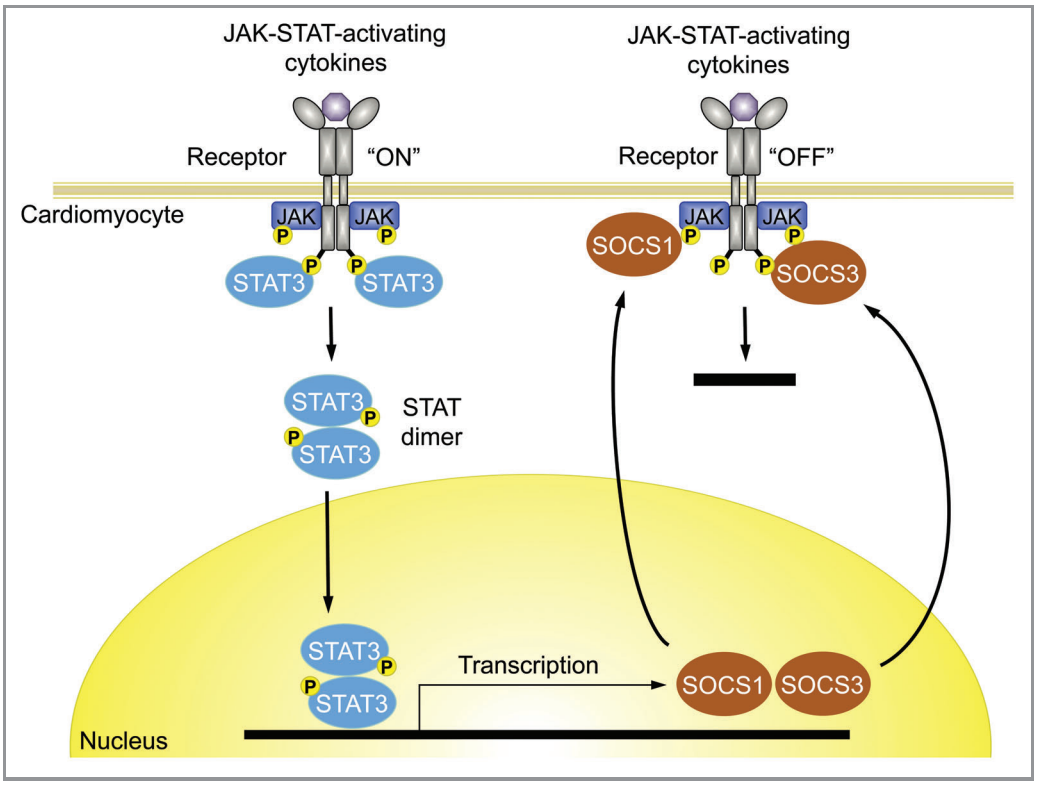

Figure 1. Negative-feedback regulation through SOCS tightly regulates the duration and intensity of cytokine-induced JAK-STAT signaling. The binding of cytokines to their receptors mediates oligomerization of the receptors, which in turn induces JAK kinase activation. The activated JAK kinases phosphorylate the cytokine receptors, leading to the recruitment and subsequent activation of STAT family proteins. The activated STAT proteins translocate into the nucleus and activate transcription of a range of cytokine-responsive genes, including SOCS genes. SOCS1 directly binds to JAK and SOCS3 binds to JAK through cytokine receptors to inhibit JAK kinase activity. These result in the shutoff of cytokine-mediated STAT activation and the subsequent transcription of cytokine-responsive genes.

SOCS3 studies regarding cardioprotection against myocardial injury.

Structure and Function of SOCS Proteins

The SOCS proteins comprise a family of eight intracellular proteins: cytokine-inducible SH2 protein (CIS), and SOCS1–SOCS7. Each SOCS family protein is characterized structurally by a central SH2 domain, an N-terminal domain of variable length and sequence, and a C-terminal 40-amino-acid conserved module known as the SOCS box (**Fig. 2**).[24-26] The SOCS box functions to recruit an E3 ubiquitin ligase complex consisting of the adaptor proteins elongins B and C, Rbx2 and the scaffold protein Cullin-5. In general, the SOCS box-containing proteins are thought to act as substrate-recognition modules to mediate the polyubiquitination and subsequent degradation of substrate proteins by the 26S proteasome.[27,28] The central SH2 domain determines the target of each SOCS protein. The SH2 domain of SOCS1 specifically binds to the tyrosine residue 1007 (Y1007) in the activation loop of JAK2, whose phosphorylation is essential for the activation of JAK2 kinase activity.[29] The SH2 domains of CIS, SOCS2 and SOCS3 bind to phosphorylated tyrosine residues on activated cytokine receptors.[9,30] SOCS3 binds to gp130-related cytokine receptors, including the phosphorylated Tyr757 residue of gp130, and Tyr985 of the leptin receptor.[31-33]

Functionally, among the family, SOCS1 and SOCS3 negatively regulate the JAK-STAT pathway by inhibiting JAK kinase

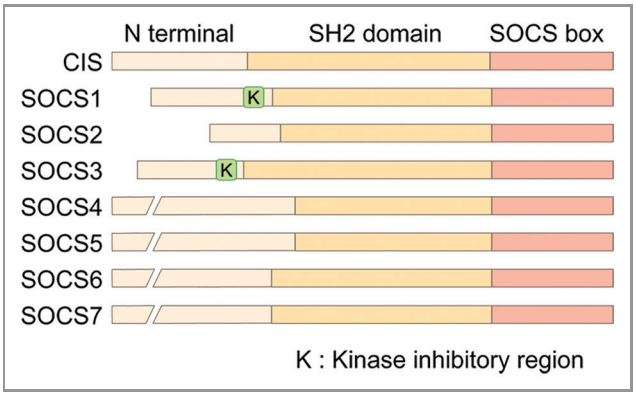

Figure 2. All of the eight SOCS family members have a central SH2 domain, an N-terminal domain of variable length and a 40-amino-acid motif at the carboxyl terminus that is known as the SOCS box. In SOCS1 and SOCS3, a kinase inhibitory region (K) adjacent to the SH2 domain that is required for high-affinity binding to JAKs and the inhibition of JAK kinase activity has also been defined.

activity. We identified a kinase inhibitory region (KIR) composed of 12 amino acids in the N-terminal domain of SOCS1 and SOCS3 that are required for the inhibition of JAK signaling and kinase activity.[29,31] We previously proposed that the KIR of SOCS1 and SOCS3 functioned as a pseudosubstrate for JAK kinase.[29,31] Recently, Babon et al. reported the novel inhibition mechanism of SOCS3 by employing nuclear magnetic resonance and classical enzyme kinetics.[34,35] They showed that SOCS3 binds to the surface of the JAK2 kinase domain, which contains a conserved three-residue GQM motif on the JAKs and induces a conformational change in the catalytic pocket, which blocks the transfer of a phosphate group to the substrate.[34,35] This information will provide clues to develop novel types of JAK inhibitors.

SOCS and Cardiac Hypertrophy

The common receptor component of the IL-6 family of cytokines, gp130, has been demonstrated to play an important role in cardiac hypertrophy.[36-39] The gp130 cytokines (e.g., CT-1 and LIF) are potent inducers of cardiomyocyte hypertrophy.[39-42] SOCS1 and SOCS3 are not expressed in steady-state of myocardium. Gp130 cytokines rapidly (within 30 min) and strongly induce SOCS3 but not SOCS1 mRNA in cardiomyocytes.[43] SOCS1 is induced by IFNγ but not by gp130 cytokines in cardiomyocytes.[43] Thus, gp130 cytokines specifically induce SOCS3, while IFNγ induces SOCS1 in cardiomyocytes. SOCS3 is markedly induced not only during the acute response phase, but also during the hypertrophic response phase after pressure overload; this late-phase SOCS3 induction is closely correlated with embryonic gene activation, including atrial natriuretic factor (ANF) and brain natriuretic peptide (BNP), suggesting that cardiac gp130-STAT3 signaling is precisely controlled by SOCS3.[43] Adenovirus-mediated gene transfer of SOCS3 to cardiomyocytes markedly suppressed the LIF-induced hypertrophic response.[43] Gp130 downstream signaling pathways, STAT3, extracellular-signal-regulated kinases 1 and 2 (ERK1/2), and AKT activation, which are coinduced by LIF stimulation, were completely suppressed by SOCS3 overexpression. Thus, during the progression of cardiac hypertrophy, SOCS3 participates in a negative feedback loop that switches off the gp130-STAT3 signaling pathway. In fact, left ventricular hypertrophy after acute pressure overload was significantly increased in cardiac-specific SOCS3-knockout mice (SOCS3-CKO).[44] Activation of STAT3, AKT and ERK1/2 were also increased in SOCS3-CKO hearts after pressure overload.[44] However, echocardiography unexpectedly revealed that cardiac function was significantly decreased, with left ventricular chamber dilation in SOCS3-CKO mice compared with control mice after pressure overload.[44] Cardiac-specific gp130 knockout mice display rapid-onset dilated cardiomyopathy and massive myocyte apoptosis during pressure overload.[45] Therefore, the delicate balance between the activation of gp130 signaling and the induction of its negative feedback regulator, SOCS3, might be important to maintenance of cardiac function during pressure overload.

SOCS1 expression is not induced after acute pressure overload.[43] However, SOCS1 expression is induced in the myocardium during chronic pressure overload.[46] Adeno-associated virus (AAV)-mediated overexpression of SOCS1 markedly worsened cardiac remodeling and function after chronic pressure overload,[46] suggesting that SOCS1 may be involved in the mechanism of maladaptive hypertrophy and failure in response to chronic pressure overload.

SOCS and Viral Myocarditis

Enteroviral infection, including coxsackievirus B3 (CVB3) infection, is a common cause of acute myocarditis, which can lead to heart failure, arrhythmias, and death.[47,48] Both a direct viral cytopathic effect and activation of the host cellular immune response play an important role in enteroviral-mediated myocardial injury. Viral infection induces the expression of JAK-STAT-activating cytokines (e.g., IFN-α/β and IFN-γ), gp130-related cytokines (e.g., CT-1 and IL-6) and IL-10 at the early stages of myocarditis.[49-51] STAT1 and STAT3 are strongly activated three days after CVB3 infection.[52] SOCS1 and SOCS3 are also strongly expressed at a similar time as the activation of STATs, indicating activation of the JAK-STAT-SOCS circuit at this early time point of CVB3 infection in the heart.[52] Because SOCS1 induction has been correlated with the induction of IFNγ-inducible genes, including interferon regulatory factor 1 (IRF1) and Fc-gamma receptor 1 (FcγRI), it is likely that SOCS1 is induced in myocardium during viral myocarditis through IFNγ-STAT1 signal activation.[52] To understand the in vivo significance of the SOCS1 expression in the cardiac myocyte, transgenic mice that express SOCS1 under the direction of the α-myosin heavy chain promoter were infected with CVB3. Cardiac myocyte-specific transgenic expression of SOCS1 inhibited enterovirus-induced activation of the JAK-STAT pathway, with accompanying increases in viral replication, cardiomyopathy and mortality in CVB3-infected mice.[52]

Like SOCS1, SOCS3 overexpression in the transgenic cardiac myocyte has a marked effect on the susceptibility of the heart to CVB3 infection.[53] SOCS3 overexpression does not inhibit IFN-receptor signaling or the IFN antiviral effect in isolated cardiomyocytes,[53] suggesting that the gp130 signaling pathway regulated by SOCS3 might be centrally involved in the prevention of CVB3-induced myocardial injury. We demonstrated that cardiac-specific knockout of gp130 increases susceptibility to CVB3.[53] Because expression of the SOCS transgenes or deletion of the gp130 gene were limited to cardiac myocytes without expression in immune cells, these results clearly demonstrate a crucial role for innate immune mechanisms that can be affected by SOCS within the cardiac myocyte. We demonstrated that inhibition of SOCS1 and SOCS3 in the cardiac myocyte through adeno-associated virus (AAV)-mediated expression of a dominant-negative SOCS1 increased the myocyte resistance to the acute cardiac injury caused by CVB3 infection in vivo, indicating that strategies aimed at inhibiting SOCS1 and SOCS3 could potentiate the intrinsic antiviral actions of cytokines that stimulate the JAK-STAT pathway.[52]

SOCS and Myocardial Infarction

Left ventricular remodeling depresses cardiac performance, contributes to the development of heart failure and is an

independent determinant of morbidity and mortality after MI.[54,55] The administration of cytokines such as G-CSF, EPO, IL-11 and LIF was recently demonstrated to prevent the development of left ventricular remodeling after MI in animals.[56-60] These cytokines activate the JAK-STAT pathways, which has a protective roles in the development of left ventricular remodeling after MI.[38,61,62] We showed that cardiac-specific deletion of SOCS3 prevents left ventricular remodeling after MI.[23] Although the initial infarct size after coronary occlusion was comparable between SOCS3-CKO and control mice, the infarct size 14 d after MI was remarkably inhibited in SOCS3-CKO mice, indicating that the progression of left ventricular remodeling after MI was prevented in SOCS3-CKO hearts.[23] Multiple JAK-STAT-activating cytokines, including LIF, G-CSF, IL-11, IL-6 and SOCS3, were strongly expressed in the heart after MI, demonstrating the presence of a cytokine-rich microenvironment in the ischemic myocardium.[23] The duration and intensity of multiple cardioprotective signaling pathways including STAT3, AKT and ERK1/2, were enhanced in SOCS3-CKO hearts. Cardiac-specific SOCS3 deletion inhibited myocardial apoptosis and fibrosis, and also augmented the expression of antioxidants, including manganese superoxide dismutase and heme oxygenase-1.[23] Myocardial SOCS3 may be a key molecule in the development of left ventricular remodeling after MI.

Wegrzyn et al. demonstrated a novel function of serine-phosphorylated STAT3 in mitochondrial homeostasis.[63] They reported that serine-phosphorylated STAT3 was present in the mitochondria of primary tissues including the heart, and that the activities of complexes I and II of the electron transport chain were significantly decreased in STAT3-deficient cells.[63] We have shown that the release of cytochrome c from mitochondria to the cytosol was prevented in the heart of SOCS3-CKO mice after MI.[23] Both tyrosine-phosphorylated STAT3 and serine-phosphorylated STAT3 were enhanced in SOCS3-CKO hearts after MI. Furthermore, mitochondrial transcription factor A (TFAM) (an essential molecule for the transcription and replication of mitochondrial DNA)[64] and proliferator-activated receptor gamma coactivator 1 (PGC-1) (an important regulator of mitochondrial biology in the heart)[65] were transiently upregulated after MI, and their expression was enhanced in SOCS3-CKO hearts.[23] Since STAT3 is present not only in the mitochondria but also in the cytosol, enhancement of STAT3 phosphorylation by cardiac-specific deletion of SOCS3 may prevent myocardial apoptosis through both the mitochondrial pathway and cytosolic/nuclear signal transduction after MI.[66]

SOCS Confers Cytokine Resistance

Resistance to cytokines limits their intrinsic efficacy. The effectiveness of IFN therapy has been demonstrated for a wide variety of tumor cells. However, some patients are resistant to IFN therapy.[67] We reported that SOCS1 and SOCS3 are highly expressed without cytokine stimulation and that cytokine-induced JAK-STAT activation is markedly reduced in IFN-resistant leukemia cell lines, suggesting that reduced activation of JAK by aberrant induction of SOCS1 or SOCS3 might be a mechanism underlying IFN resistance.[68] Leptin is an adipocyte-derived hormone that is centrally involved in energy homeostasis.[69] Resistance to leptin is a feature of most cases of obesity human and rodents.[69] We and another group demonstrated that SOCS3 deficiency in the brain elevates leptin sensitivity, and that leptin confers resistance to diet-induced obesity.[21,70] Similarly, we demonstrated that the induction of SOCS1 or SOCS3 by pretreatment with CT-1 in vivo confers resistance to subsequent CT-1 administration.[71] These findings indicate that SOCS1 and SOCS3 expression confers resistance to cytokines action. SOCS1 and SOCS3 induction is an important mechanism underlying the cytokine resistance. In other words, SOCS1 and SOCS3 are promising therapeutic targets for cytokine resistance in the context of diseases.

While JAK-STAT-activating cytokines, including EPO and G-CSF, improved left ventricular remodeling and function after MI in animals,[56-60] the effect of cytokines on left ventricular remodeling and function in these patients remains controversial. The first phase II trial showed that intravenous bolus of EPO did not reduce infarct size in patients with MI.[72] The timing of the treatment is considered important to obtain the most beneficial effects of cytokine therapy in MI patients.[73] SOCS3 is markedly induced not only by ischemia, but also by administered cytokine itself during MI. Therefore, ischemia-induced SOCS3 may reduce the effect of cytokine therapy in patients with MI, suggesting that SOCS3 confers cytokine resistance in human. In fact we demonstrated that myocardial-specific SOCS3 deletion enhances multiple cardioprotective signaling pathways and ameliorates left ventricular remodeling after MI.[23] Small-molecule antagonists of SOCS3 or tissue-specific vector delivery of SOCS3 inhibitor during left ventricular remodeling after MI may prove to be a clinically valuable strategies to enhance the protective effect of JAK-STAT-activating cytokines. We propose that SOCS3 may serve as a novel therapeutic target to prevent left ventricular remodeling in patients with MI.

Concluding Remarks

During the past decade, since the discovery of the SOCS family proteins, we have extended our understanding of the structure and function of these proteins. SOCS proteins have been revealed as key negative regulators of cytokine and growth factor signaling. The generation of mice lacking individual SOCS genes has been instrumental in defining the role of individual SOCS proteins in specific cytokine pathways. Furthermore, tissue-specific SOCS knockout mice have revealed the important roles of SOCS proteins in the pathogenesis of diseases.

SOCS molecules positively and negatively regulate macrophage and dendritic-cell activation and are essential for T-cell development and differentiation. Given that immune-mediated inflammation is substantially involved in the pathogenesis of myocardial diseases (e.g., MI or heart failure), SOCS molecules within leukocytes remain to be elucidated in the context of myocardial diseases pathogenesis.

In the heart, JAK-STAT3-activating cytokines have cardioprotective roles through anti-apoptosis, inhibition of mitochondrial

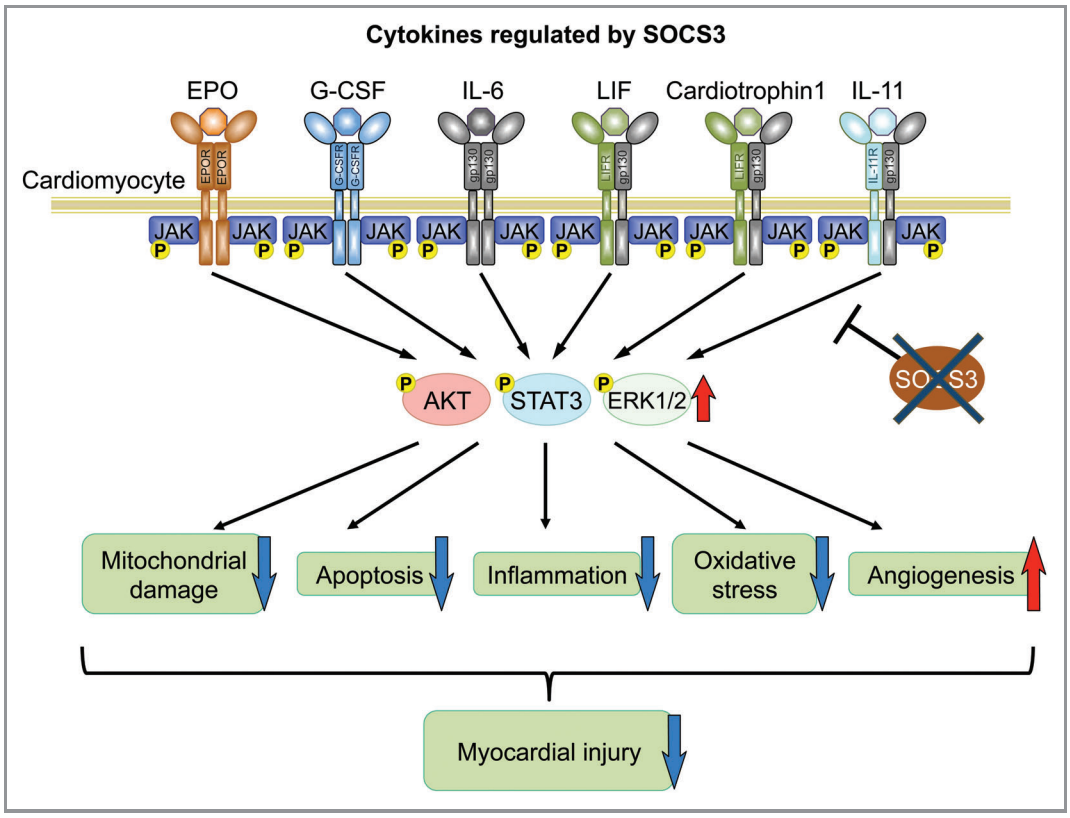

Figure 3. The mechanism underlying the inhibition of myocardial injury in cardiac-specific SOCS3-deficient mice. Multiple JAK-STAT-activating cytokines including G-CSF, LIF, CT-1, IL-6 and IL-11, are induced in injured myocardium. SOCS3 deletion in cardiomyocytes enhances cardioprotective signaling pathways, including STAT3, AKT and ERK1/2 pathways, which inhibit myocardial apoptosis, mitochondrial damage, oxidative stress and inflammation and promote angiogenesis, resulting in the prevention of myocardial injury.

damage and oxidative stress, anti-inflammation, and angiogenesis (**Fig. 3**). Because SOCS1 and SOCS3 are potent suppressors of the JAK-STAT3 signaling pathway, the strategy of SOCS inhibition has several merits for cardioprotection. We must develop a carrier (e.g., nanoparticle) that is capable of delivering a SOCS3-antagonizing small molecule or siRNA into myocardium in vivo.

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